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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/776,989	02/11/2004	Scott Saunders	101353-232	5871

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EXAMINER	
LUCAS, ZACHARIAH	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 05/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/776,989	SAUNDERS ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *5-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2-11-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, and to embodiments wherein the second polypeptide portion of the claimed fusion protein is GMCSF, in the reply filed on March 7, 2005 is acknowledged. The traversal is on the ground(s) that a single search would be sufficient for the full scope of the claimed proteins. This is not found persuasive because the claims are drawn to fusion proteins comprising many different proteins, a search for one of which would not necessarily be sufficient to demonstrate the patentability of each of the various claimed proteins.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 5-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on March 7, 2005.

3. Claims 1-4, 15, and 16 are pending and under consideration.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on February 11, 2004 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

The following reference is in a foreign language accompanied by an English abstract. Due to this, the reference has been examined only to the extent of the disclosure in the abstract.

WO 90/07712.

Specification

5. The disclosure is objected to because of the following informalities: On pages 50 of the application, the specification refers to "transforming growth factor- χ (TGF- β)." The disclosure is objected to as it is not clear what TGF is being referred to.

Appropriate correction is required.

6. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: there is no antecedent basis support in the application for either a heparin sulfate attachment site comprising amino acids 20-41 of SEQ ID NO: 9, or fusion proteins thereof. While the specification identifies the region of residues 31-40 of SEQ ID NO: 9 as such an attachment site (pages 34-36), there is no support in the written description (other than the originally filed claims) for polypeptides comprising amino acids SEQ ID NO: 20-41 of SEQ ID NO: 9. Appropriate correction is required.

Note: because the claim language was present in the original claims of the application, this is not a rejection for lack of written description. This is an objection to the specification for not providing antecedent basis for the claim language.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-4, 15, and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention to the full extent of the claims. The claims recite a fusion protein comprising a first polypeptide portion having a sequence from a syndecan protein and including a heparan sulphate attachment sequence (with a heparan sulphate attached thereto) comprising amino acids 20-41 of SEQ ID NO: 9, or amino acids 20-41 with conservative amino acid substitutions. Claim 2 further limits the proteins to those comprising a sequence "at least 50% identical to amino acids 20-41 of SEQ ID NO: 9." The specification, while being enabling for fusion polypeptides comprising the residues 20-41 of SEQ ID NO: 9, and for fragments thereof that comprise the Xac-Z-Ser-Gly-Ser-Gly heparan sulfate (HS) binding sequence (SGSG sequence) described on page 4 of the specification, the claims are not enabling for any peptide of residues 20-41 of SEQ ID NO: 9 with any number of conservative substitutions therein. This is especially true for substitutions in the SGSG sequence.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of

those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered. Those factors considered relevant in the present case are the breadth of the claims, the number of examples and amount of guidance presented, and the predictability of the art.

The scope of the claims has been described above. The rejected claims, other than claim 2, make no limit on the number of substitutions that may be made to the sequence. Although the sequence is only about 20 amino acids in length, this still leads to a group of potential proteins of over (at least) a million sequences. Thus, the breadth of the claims is great. Further, the applicant has not shown that sequences with 70 or 80 percent identity with the claimed sequence retains the ability to bind HS, much less peptides with 50% or less identity.

No guidance is given as to which substitutions may be made other than that only conservative substitutions may be made (claim 17). This lack of guidance is extremely important given the level of unpredictability in the art of protein modification. In the article "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," the authors state that "at some positions many different, nonconservative, amino acid substitutions were allowed," however "[a]t other positions, no substitutions or only conservative substitutions were allowed." Bowie et al., Science 247, 1306-1310, at 1306. The sequences that were less tolerant to substitutions, like those of the claimed peptide, were those of an active site.

Additionally, of the potential substitution mutants of the peptide, this includes over 10,000 possible substitution mutants of the SGSG sequence. The applicant has not shown that any substitution mutant of the SGSG sequence could be made without affecting the ability of the

peptide to bind HS. As the applicant has taught only the SGSG sequence as a heparan sulfate-binding site, the applicant is not enabled for any peptide according to the claims that can bind HS, other than those comprising the SGSG sequence. Although Bowie (above) does indicate that active sites are sometimes tolerant to conservative substitutions, the applicant has not shown such to be the case in the claimed protein.

Due to the breadth of the claims, the unpredictability of the art, and the lack of guidance provided by the applicant, and because the utility of the claimed fusion protein depends on the presence of the heparan sulphate, the applicant is not enabled for claims to a fusion protein that can comprise any number of substitutions. Nor is the applicant enabled for peptides with even one substitution in the SGSG sequence.

9. Claims 1-4, 15, and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims read on a genus of inventions comprising any variant of SEQ ID NO: 9, or variants of down to 50% identity thereto, which maintain the ability of SEQ ID NO: 9 to bind to heparan sulfate.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical

> and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions, the specification must provide written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed.

As noted above, the present claims read on a genus of fusion proteins comprising variants of SEQ ID NO: 9 that have the ability to bind heparan sulfate. However, the teachings of the specification teach that the SGSG sequence identified above is required for this binding. Page 4. There is no identification of other sequence, or modified versions of this sequence, that would also be capable of binding to heparan sulfate. Thus, while the application provides descriptive support for heparan sulfate attachment sequences comprising SEQ ID NO: 9, or variants thereof maintaining the SGSG sequence, the application does not provide support for the claims to the extent that they read on any variant of SEQ ID NO: 9 that does not comprise the SGSG sequence.

10. Claim 3 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for fusion proteins comprising residues 20-41 of SEQ ID NO: 9 that bind to chondroitin sulfate in addition to heparan sulfate, does not reasonably provide enablement for any variant of the sequence that maintains chondroitin sulfate binding activity. The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. As indicated above, the present claims read on any of the modified forms of the heparan sulfate attachment sequence of SEQ ID NO: 9, wherein the further comprising at least one chondroitin sulfate attachment site. The factors to be considered when making a determination regarding the scope of enablement have been identified above. In the present case, the scope of the claims, the guidance and examples provided, and the predictability of the art are considered the relevant factors.

This claim is rejected on substantially similar grounds as were described with respect to the scope of heparan sulfate attachment sites in claims 1-4, 15, and 16 above. With reference to the chondroitin sulfate attachment site, the application identifies only three putative sites; those of residues 37, 207, and 217 of SEQ ID NO: 1. App. page 70. The sequence surrounding residue 37 is present in the sequence residues 20-41 of SEQ ID NO: 9. Thus, it would appear that this sequence would be capable of binding to chondroitin sulfate. However, with the exception of the putative identification of residues 207 and 217, there is no identification of any other chondroitin sulfate attachment sequences, nor any demonstration of what residues in and around SEQ ID NO: 37 may be required for, or modified without destroying, the proteins chondroitin binding activity. In view of the limited guidance, and the unpredictability in the art as described previously, while the application is enabling for fusion proteins comprising SEQ ID NO: 9 that bind chondroitin sulfate, the application is not enabling for any variant thereof that also maintains this binding activity.

11. Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This claim has been described above. As indicated above, the claim reads on any fusion protein comprising SEQ ID NO: 9 that is able to bind to chondroitin sulfate. However, while the application has provided sufficient information to indicate that SEQ ID NO: 9 would be capable of binding to chondroitin sulfate, the claims do not provide sufficient support for any variant of this sequence that maintains this activity. The application provides only a single example of the sequence, and does not identify which residues other than the serine at position 37 ware required for such binding.

As indicated above, the identification of a claimed genus by function alone is not sufficient written description support for that genus. In the present case, only a single example of fusion proteins falling within the scope of the claimed genus has been described (those comprising SEQ ID NO: 9). The claims have identified the claimed genus only by identification of a function, and do not provide any structural requirement shown, or known, to correlate with the chondroitin sulfate binding function. The claims are therefore rejected as lacking sufficient written description support for fusion proteins comprising any variant of SEQ ID NO: 9 that binds to chondroitin sulfate.

Conclusion

12. No claims are allowed.

13. The following prior art reference is made of record and considered pertinent to applicant's disclosure. However, while relevant they are also not used as a basis for rejection for the stated reasons.

> Murdoch et al., J Biol Chem 267: 8544-57. This reference provides teachings regarding the heparan sulfate binding sequences of human proteoglycans. See e.g., abstract, and pages 8546 (right column- Domain I). However, the reference does not teach or suggest a fusion protein according to the present claims.
>
> Roberts et al., Nature 332: 376-78. This reference teaches that association of GM-CSF with heparan sulfate, but does not teach a fusion protein described by the present claims.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Z. Lucas
Patent Examiner

James C. Housel 4/16/05

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